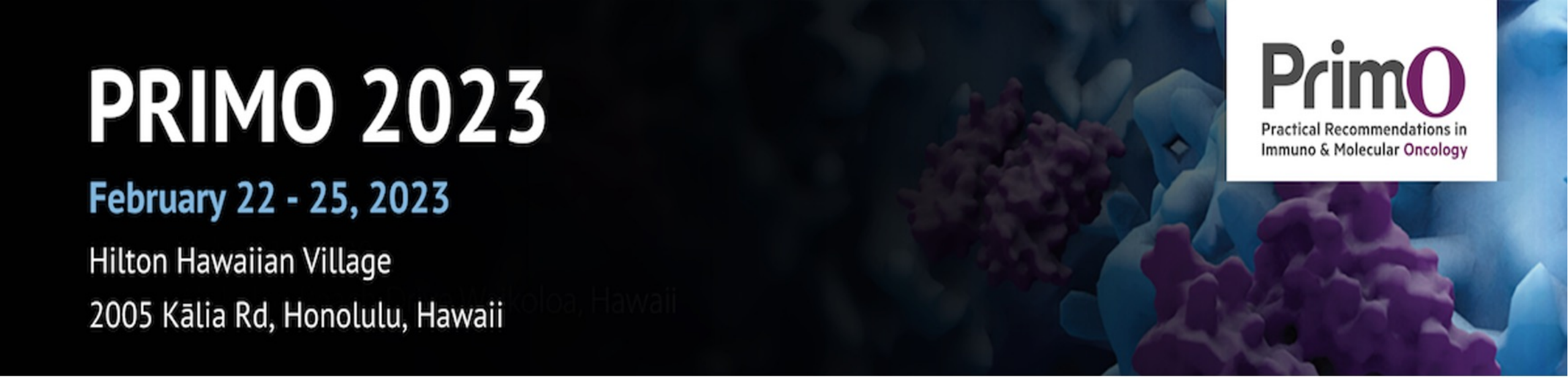

Other Targetable Agents (K-Ras^{G12C}, RET, B-Raf^{V600E}, and NTRK)

Edgardo S. Santos Castillero, M.D., FACP
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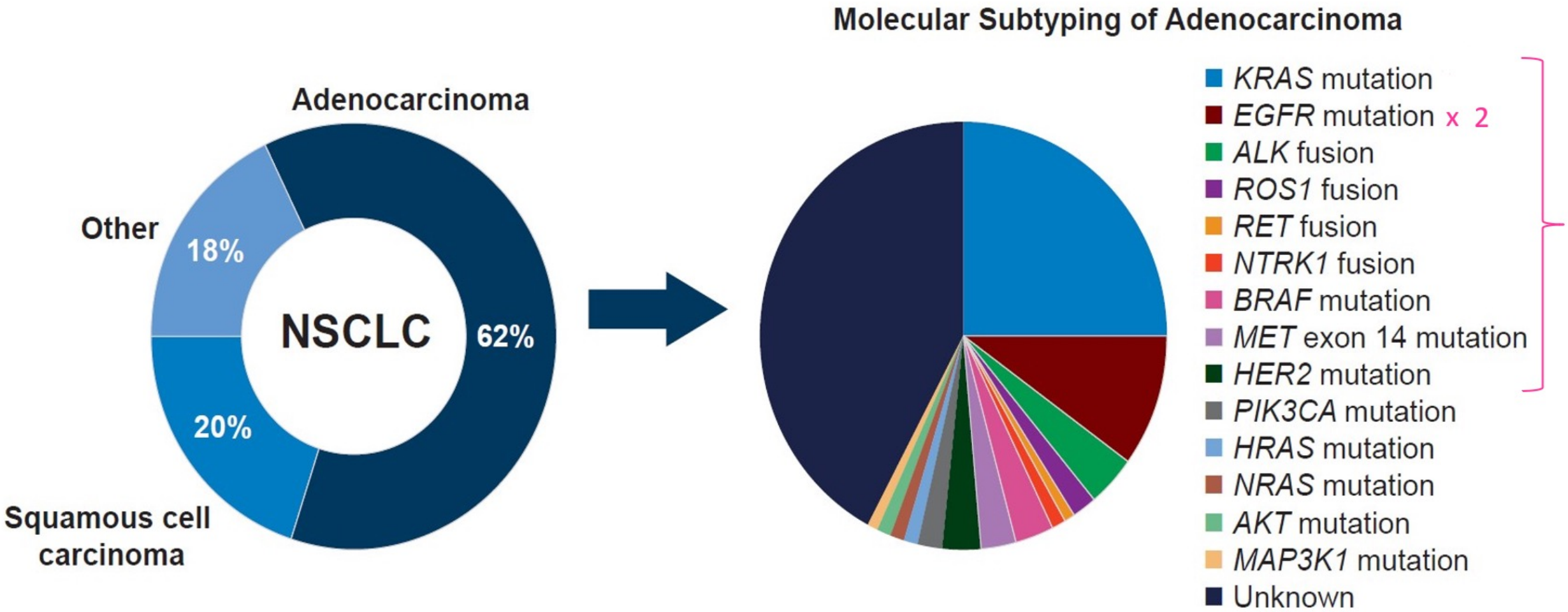
FLASCO Treasurer & FLASCO Foundation President

February 24, 2023

PrimO
Practical Recommendations in
Immuno & Molecular Oncology

Targeted Therapy in NSCLC



Targeted Therapy for Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

MOLECULAR AND BIOMARKER-DIRECTED THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

***EGFR* Exon 19 Deletion or Exon 21 L858R**
- First-line therapy
  - Afatinib[1]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6]
  - Erlotinib + ramucirumab[7]
  - Erlotinib + bevacizumab[c] (nonsquamous)[8]
- Subsequent therapy
  - Osimertinib[9]

***EGFR* S768I, L861Q, and/or G719X**
- First-line therapy
  - Afatinib[1,10]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6,11]
- Subsequent therapy
  - Osimertinib[9]

***EGFR* Exon 20 Insertion Mutation**
- Subsequent therapy
  - Amivantamab-vmjw[12]
  - Mobocertinib[13]

***KRAS* G12C Mutation**
- Subsequent therapy
  - Sotorasib[14]
  - Adagrasib[15]

***ALK* Rearrangement**
- First-line therapy
  - Alectinib[16,17]
  - Brigatinib[18]
  - Ceritinib[19]
  - Crizotinib[16,20]
  - Lorlatinib[21]
- Subsequent therapy
  - Alectinib[22,23]
  - Brigatinib[24]
  - Ceritinib[25]
  - Lorlatinib[26]

***ROS1* Rearrangement**
- First-line therapy
  - Ceritinib[27,28]
  - Crizotinib[29]
  - Entrectinib[30]
- Subsequent therapy
  - Lorlatinib[31]
  - Entrectinib[30]

***BRAF* V600E Mutation**
- First-line therapy
  - Dabrafenib/trametinib[32]
  - Dabrafenib[32]
  - Vemurafenib
- Subsequent therapy
  - Dabrafenib/trametinib[33,34]

***NTRK1/2/3* Gene Fusion**
- First-line/Subsequent therapy
  - Larotrectinib[35]
  - Entrectinib[36]

***MET* Exon 14 Skipping Mutation**
- First-line therapy/Subsequent therapy
  - Capmatinib[37]
  - Crizotinib[38]
  - Tepotinib[39]

***RET* Rearrangement**
- First-line therapy/Subsequent therapy
  - Selpercatinib[40]
  - Pralsetinib[41]
  - Cabozantinib[42,43]

***ERBB2 (HER2)* Mutation**
- Subsequent therapy
  - Fam-trastuzumab deruxtecan-nxki[44]
  - Ado-trastuzumab emtansine[45]

NCCN version 1.2023, 12/31/2022

GenesisCare

OLA Oncology Latin American Association

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In these assigned topics.. News since PRIMO 2022:

FDA grants accelerated approval to dabrafenib in combination with trametinib for unresectable or metastatic solid tumors with BRAF V600E mutation

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On June 22, 2022, the Food and Drug Administration granted accelerated approval to dabrafenib in combination with trametinib for the treatment of adult and pediatric patients ≥ 6 years of age with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. Dabrafenib in combination with trametinib is not indicated for patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition. Dabrafenib is not indicated for patients with wild-type BRAF solid tumors.

The safety and efficacy were evaluated in 131 adult patients from open-label, multiple cohort trials BRF117019 (NCT02034110) and NCI-MATCH (NCT02465060), 36 pediatric patients from CTMT212X2101 (NCT02124772), and supported by results in COMBI-d, COMBI-v, and BRF113928 (studies in melanoma and lung cancer already described in product labeling). Study BRF117019 enrolled patients with BRAF V600E mutation positive specific solid tumors including high grade glioma (HGG), biliary tract cancer, low grade glioma (LGG), adenocarcinoma of small intestine, gastrointestinal stromal tumor, and anaplastic thyroid cancer (ATC). NCI-MATCH Subprotocol H enrolled adult patients with BRAF V600E mutation positive solid tumors except patients with melanoma, thyroid cancer, or CRC. Parts C and D of Study CTMT212X2101 enrolled 36 pediatric patients with BRAF V600 refractory or recurrent LGG or HGG. The major efficacy outcome measure of

FDA approves selpercatinib for locally advanced or metastatic RET fusion-positive solid tumors

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On September 21, 2022, the Food and Drug Administration granted accelerated approval to selpercatinib for adult patients with locally advanced or metastatic solid tumors with a rearranged during transfection (RET) gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.

Efficacy was demonstrated in LIBRETTO-001 (NCT03157128), a multicenter, open-label, multi-cohort trial that evaluated 41 patients with RET fusion-positive tumors (other than non-small cell lung cancer and thyroid cancer) with disease progression on or following prior systemic treatment or who had no satisfactory alternative treatment options. The efficacy evaluation was supported by data in 343 patients with RET fusion-positive NSCLC and thyroid cancer enrolled in the same trial already described in product labeling. Patients received selpercatinib until disease progression or unacceptable toxicity.

The primary efficacy measures were overall response rate (ORR) and duration of response (DOR) as determined by a Blinded Independent Review Committee (BIRC). Among 41 evaluable patients, ORR was 44% (95% CI: 28, 60) with a DOR of 24.5 months (95% CI: 9.2, not estimable). Tumor types with responses included pancreatic adenocarcinoma, colorectal, salivary, unknown primary, breast, soft tissue sarcoma, bronchial carcinoid, ovarian, small intestine, and cholangiocarcinoma.

The median age of patients was 50 years (range 21 to 85). Selected demographics were as follows: 54% female; 68% White, 24% Asian, 4.9% Black; 7% Hispanic/Latino; 95% had ECOG performance status of 0 or 1; 95% had metastatic disease. Thirty-seven patients (90%) received prior systemic therapy (median 2 [range 0-9]; 32% received 3 or more). The most common cancers were pancreatic (27%), colorectal (24%), salivary (10%), and unknown primary (7%). RET fusion-positive status was detected in 97.6% of patients using NGS and 2.4% using FISH.

FDA grants accelerated approval to adagrasib for KRAS G12C-mutated NSCLC

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On December 12, 2022, the Food and Drug Administration (FDA) granted accelerated approval to adagrasib a RAS GTPase family inhibitor, for adult patients with KRAS G12C¬-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy.

FDA also approved the QIAGEN therascreen KRAS RGQ PCR kit (tissue) and the Agilent Resolution ctDx FIRST Assay (plasma) as companion diagnostics for Krazati. If no mutation is detected in a plasma specimen, the tumor tissue should be tested.

Approval was based on KRYSTAL-1, a multicenter, single-arm, open-label clinical trial (NCT03785249) which included patients with locally advanced or metastatic NSCLC with KRAS G12C mutations. Efficacy was evaluated in 112 patients whose disease has progressed on or after platinum-based chemotherapy and an immune checkpoint inhibitor, given either concurrently or sequentially. Patients received adagrasib 600 mg orally twice daily until disease progression or unacceptable toxicity.

The main efficacy outcome measures were confirmed objective response rate (ORR) according to RECIST 1.1, as evaluated by blinded independent central review, and duration of response (DOR). The ORR was 43% (95% CI: 34%, 53%) and median DOR was 8.5 months (95% CI: 6.2, 13.8).

The most common adverse reactions (≥ 20%) were diarrhea, nausea, fatigue, vomiting, musculoskeletal pain, hepatotoxicity, renal impairment, dyspnea, edema, decreased appetite, cough, pneumonia, dizziness, constipation, abdominal pain, and QTc interval prolongation. The most common laboratory abnormalities (≥ 25%) were decreased lymphocytes, increased aspartate aminotransferase, decreased sodium, decreased hemoglobin, increased creatinine, decreased albumin, increased alanine aminotransferase, increased lipase, decreased platelets, decreased magnesium, and decreased potassium.

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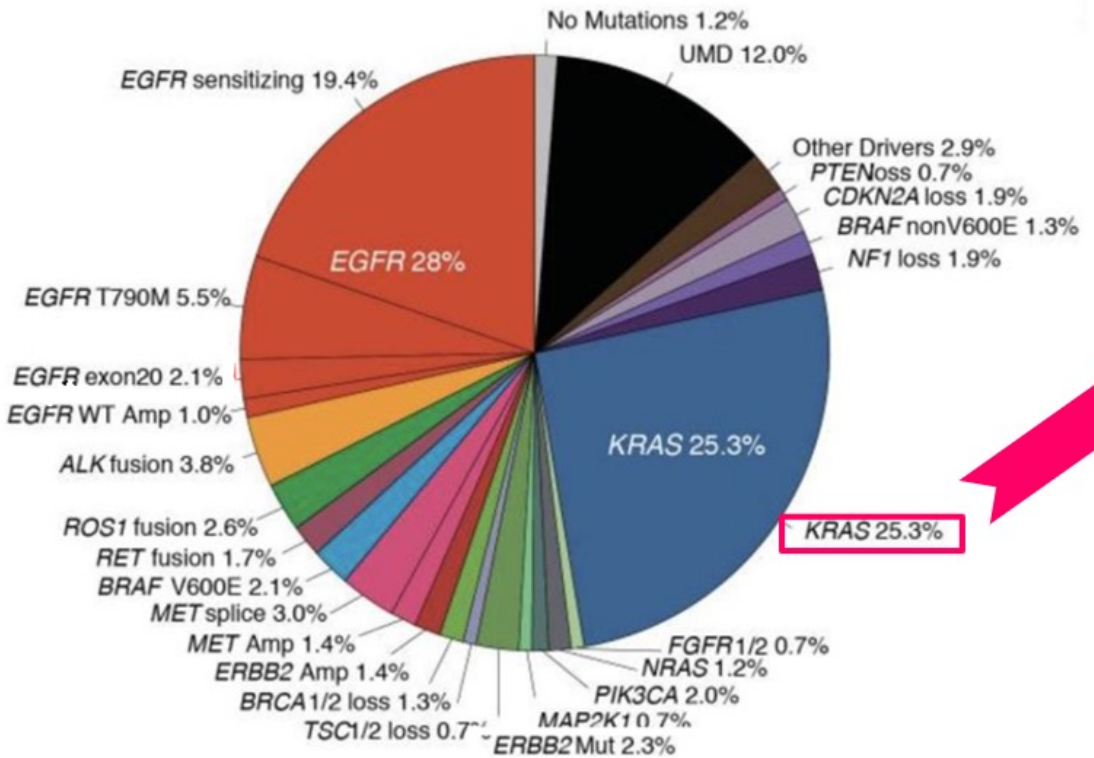
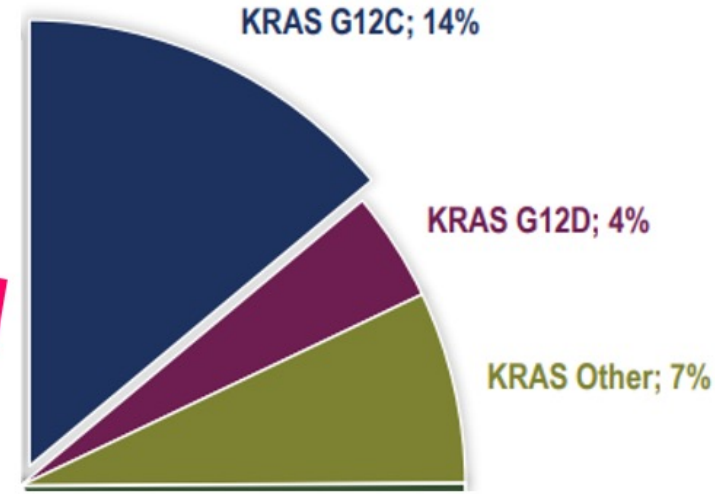
K-RAS^{G12C} Pathway





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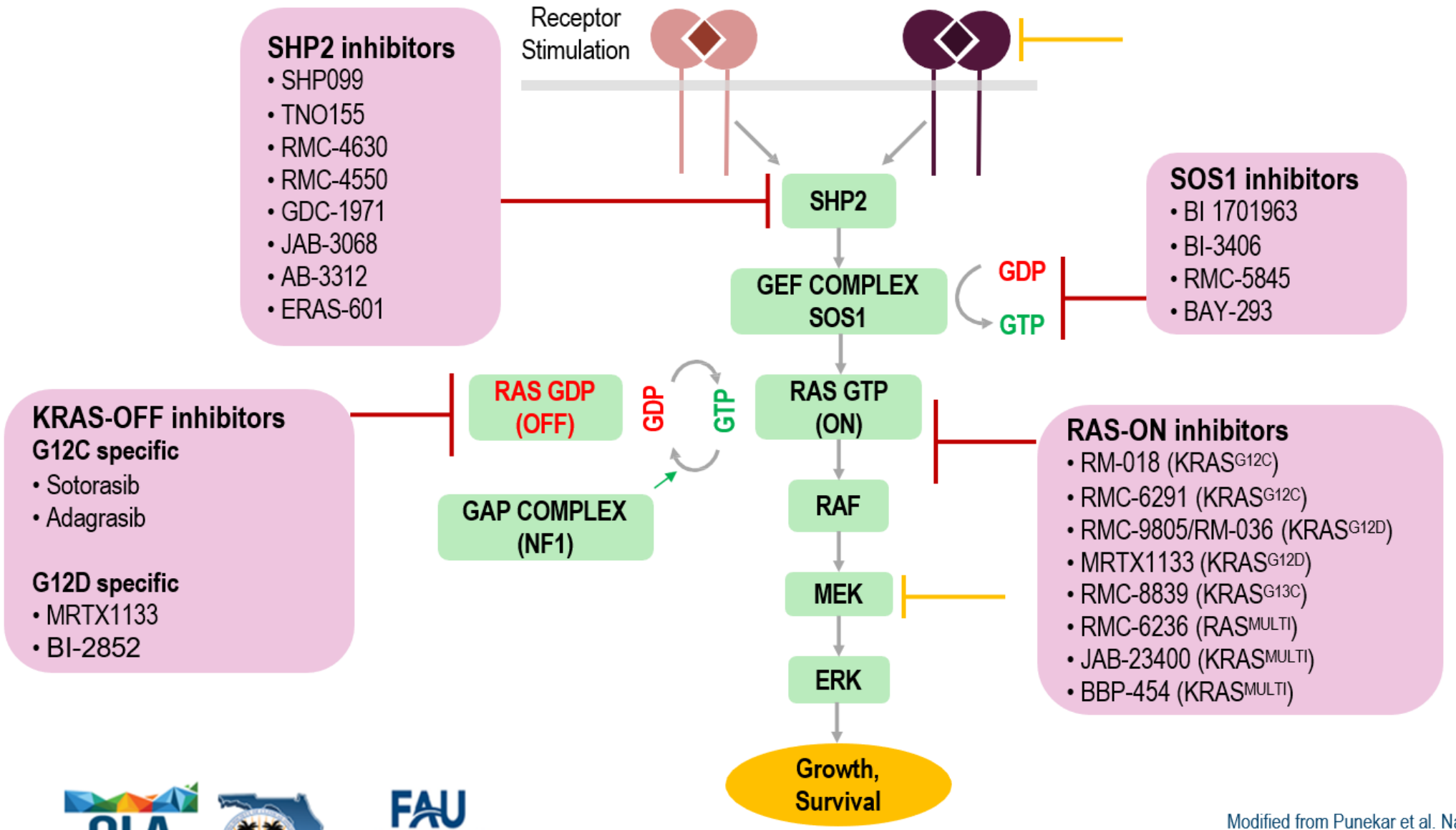
Targeting KRAS: The Beating Heart Of Cancer



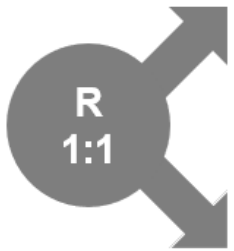
Modified from Punekar et al. Nat Rev Clin Oncol (2022) and AACR-NCI-EORTC 2019

KRAS G12C inhibitors in previously treated advanced NSCLC:

Trial design

KRAS G12C mutant NSCLC Stage IV (2L/3L)

- Prior treatment with a PD-(L)1 inhibitor and chemotherapy
- Treated brain metastases



Docetaxel

KRAS G12C inhibitor

Primary endpoint

PFS

Sotorasib	Adagrasib	JDQ443	GDC-6036
CodeBreak 200	KRYSTAL-12	KontRASt-02	BFAST (cohort G)
N=345	N=340	N=360	N=301

LBA 10: Sotorasib vs docetaxel for previously treated NSCLC with KRAS G12C mutation: CodeBreak 200 phase III study

Lead Author: M Jonhson

Date/Time: Sept 12th, 16:30 – 18:15

ClinicalTrials.gov accessed on August 30th, 2022: 1, NCT04303780; 2, NCT04685135; 3, NCT05132075; 4, NCT03178552

CodeBreaK 200 Phase 3 Study Design

Key eligibility criteria

- Locally advanced/unresectable or metastatic *KRAS* G12C-mutated NSCLC
- **≥ 1 prior treatment including platinum-based chemotherapy and checkpoint inhibitor***
- **No active brain metastases**
- ECOG performance status ≤ 1

Stratification factors

- Prior lines of therapy (1 vs 2 vs > 2)
- Race (Asian vs non-Asian)
- History of CNS involvement (yes vs no)

Randomisation 1:1 (N = 345)

Sotorasib 960 mg oral daily N = 171

Docetaxel 75 mg/m² IV Q3W N = 174

Primary Endpoint: PFS by BICR

Secondary Endpoints: Efficacy (OS†, ORR, DOR, TTR, DCR)**, safety/tolerability, PRO**

ITT population analysis included all randomised patients

Per regulatory guidance, protocol was amended to reduce planned enrolment from 650 to ~330 patients, and crossover from docetaxel to sotorasib was permitted.

Enrollment period: June 4, 2020 to April 26, 2021; protocol amendment: February 15, 2021; data cutoff: August 2, 2022.

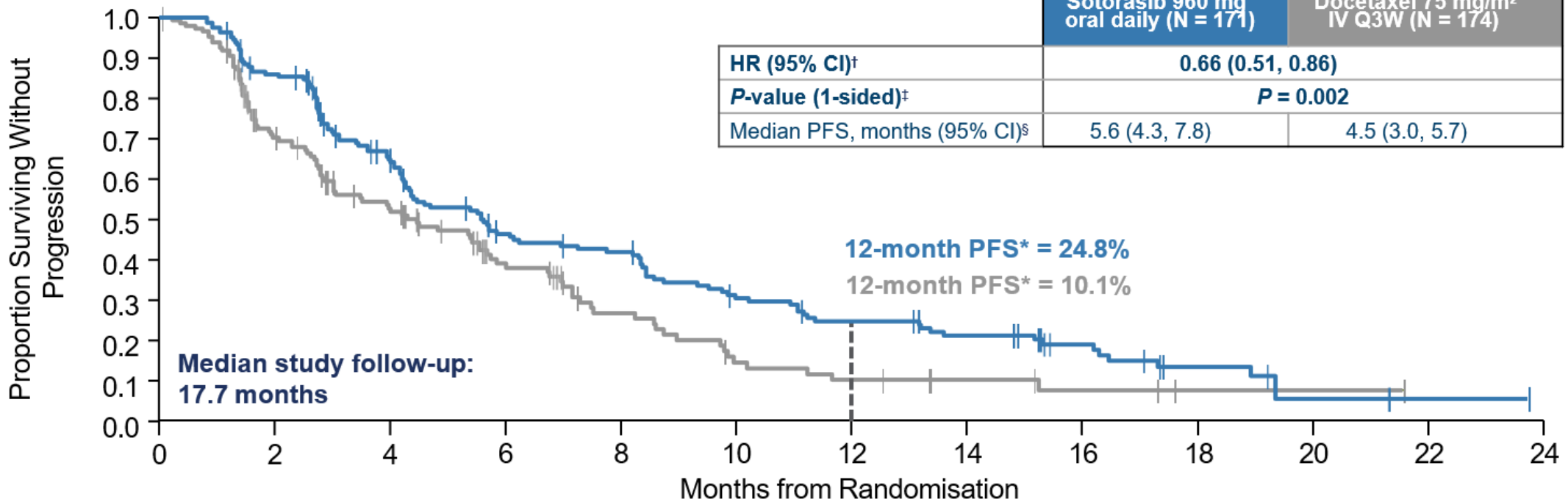
NCT04303780; EudraCT: 2019-003582-18.

*Treatment with chemotherapy and checkpoint inhibitor could be concurrent or sequential; patients with medical contraindication to these therapies could be included with approval.

†Analysis of OS planned if PFS was found to be statistically significant and when at least 198 OS events have been reached.

Melissa L. Johnson, MD. 2022 ESMO Congress, September 12; Paris, France.

Primary Endpoint: PFS by BICR



	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
HR (95% CI)†	0.66 (0.51, 0.86)	
P-value (1-sided)‡	*P* = 0.002	
Median PFS, months (95% CI)§	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)

Number of Patients at Risk:

Sotorasib	171	139	93	63	56	38	30	24	14	6	2	1	0
Docetaxel	174	93	62	36	20	10	7	5	3	1	1	0	

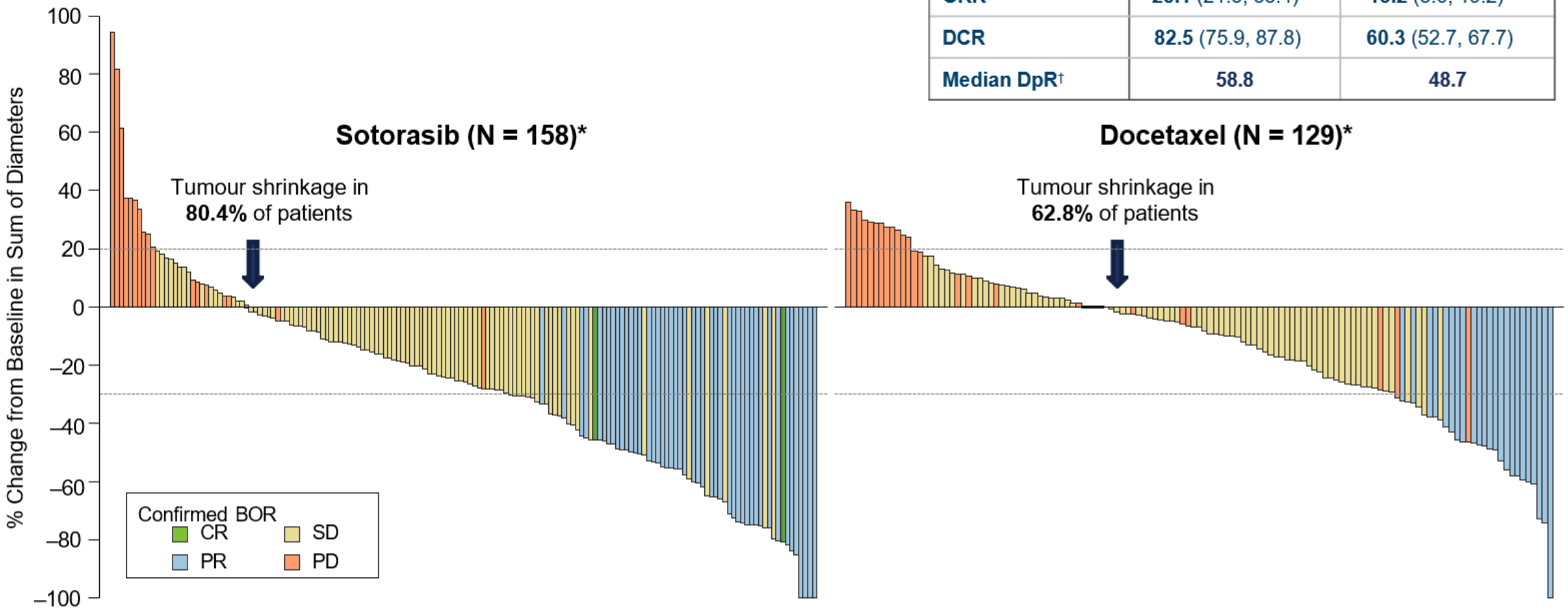
CodeBreaK 200 met its primary endpoint with sotorasib demonstrating superior PFS over docetaxel (HR 0.66, *P* = 0.002); 12-month PFS rate was 24.8% for sotorasib and 10.1% for docetaxel

*PFS rates estimated using Kaplan-Meier method; ITT population.
†HR and 95% CIs estimated using a stratified Cox proportional hazards model.
‡*P*-value calculated using a stratified log-rank test.
§Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.

Melissa L. Johnson, MD. 2022 ESMO Congress, September 12; Paris, France.

Tumour Response by BICR

% (95% CI)	Sotorasib	Docetaxel
ORR	**28.1** (21.5, 35.4)	**13.2** (8.6, 19.2)
DCR	**82.5** (75.9, 87.8)	**60.3** (52.7, 67.7)
Median DpR†	**58.8**	**48.7**



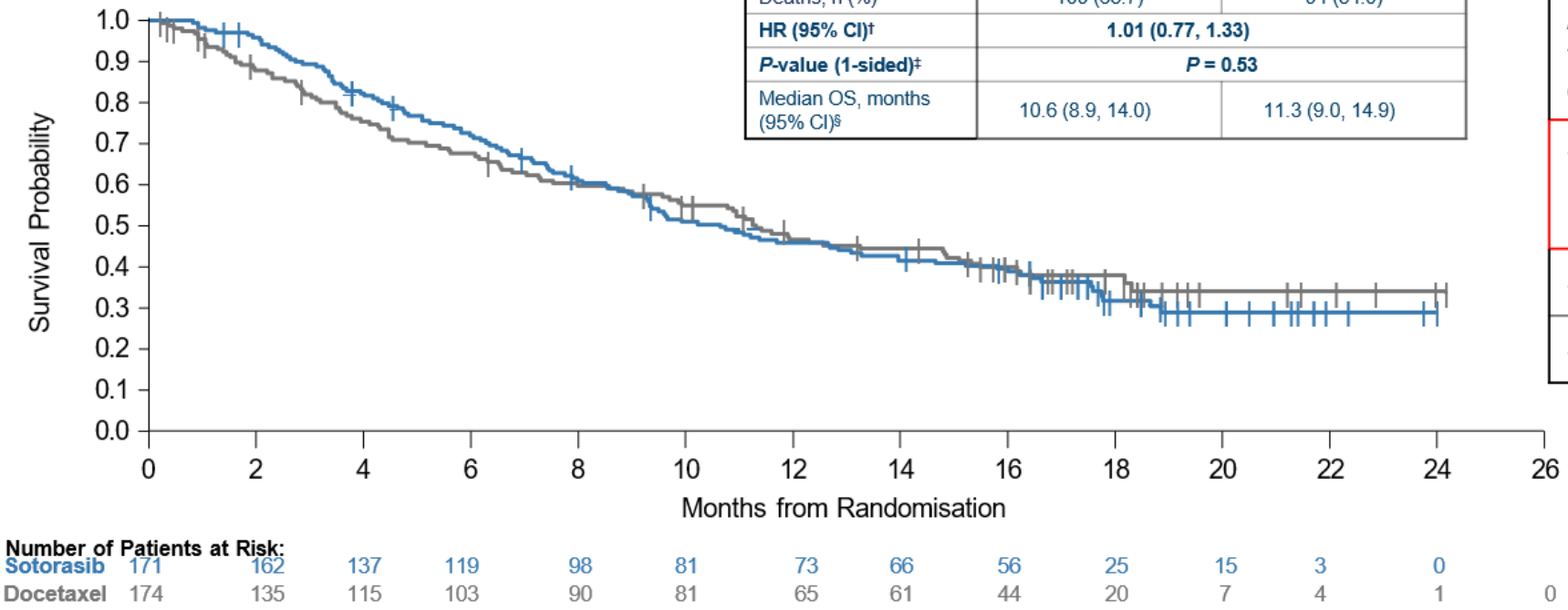
Response rate was significantly higher with sotorasib versus docetaxel ($P < 0.001$)

*Patients without baseline target lesions or post-baseline percent changes, or with BOR of NE are not shown.
†Median of best percent change from baseline in sum of diameters for confirmed responders.

Melissa L. Johnson, MD. 2022 ESMO Congress, September 12; Paris, France.

OS: Sotorasib vs Docetaxel*

	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
Deaths, n (%)	109 (63.7)	94 (54.0)
HR (95% CI)†	**1.01 (0.77, 1.33)**	
***P*-value (1-sided)‡**	***P* = 0.53**	
Median OS, months (95% CI)§	10.6 (8.9, 14.0)	11.3 (9.0, 14.9)



Number of Patients at Risk:

Sotorasib	171	162	137	119	98	81	73	66	56	25	15	3	0
Docetaxel	174	135	115	103	90	81	65	61	44	20	7	4	1	0

	Sotorasib	Docetaxel
Any subsequent treatment, including crossover**	36%	42%
Subsequent $KRAS^{G12C}$ inhibitor, including crossover	4%	34%
Subsequent chemo	21%	12%
Subsequent IO	9%	6%

*OS rates estimated using Kaplan-Meier method; ITT population.
†HR and 95% CIs estimated using a stratified Cox proportional hazards model
‡ *P*-value calculated using a stratified log-rank test.
§Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.
**Patients (16.4% in sotorasib arm, 5.2% in docetaxel arm) were treated beyond progression

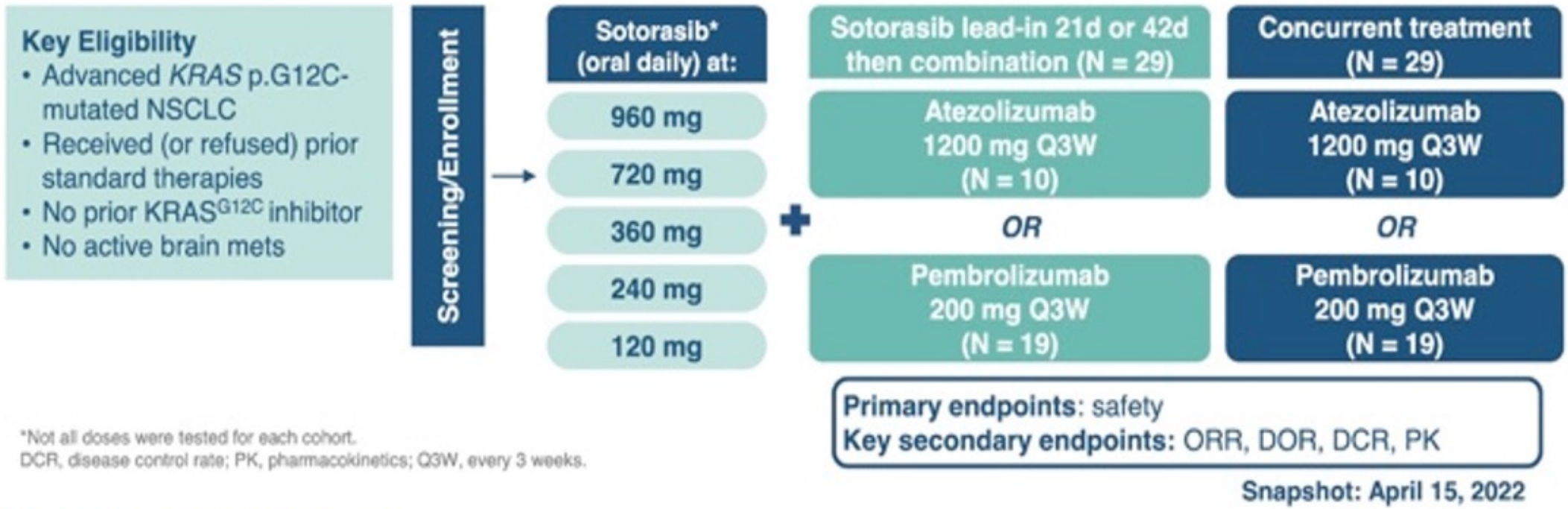
Melissa L. Johnson, MD. 2022 ESMO Congress, September 12; Paris, France.

The Competition Is On!

	CodeBreak-100	KRYSTAL-1
Dosing	960 mg daily	600 mg BID
RR	41% (2-yr analysis)	43%
PFS	6.3 (2-yr analysis)	6.5
OS	12.5	12.6
CNS	Prob	Prob
Gr 3/4 AE	33%	43%
Discontinuation rate	7%	7%
Common AEs	Diarrhea, nausea, fatigue, increased AST/ALT	Diarrhea, nausea, fatigue, anemia, dyspnea

CodeBreak 100/101: Study Design

- Phase 1b multicenter, open-label studies



Li BT et al. IASLC 2022: Abstract OA03.06.

CodeBreak 100/101: Safety for Sotorasib Lead-in + Pembrolizumab

TRAE*, n (%)	Sotorasib 120 mg (N = 3)		Sotorasib 240 mg (N = 5)		Sotorasib 360 mg (N = 11)	
	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3
All TRAEs	**3 (100)**	**3 (100)**	**3 (60)**	**1 (20)**	**9 (82)**	**6 (55)**
ALT increased	2 (67)	2 (67)	1 (20)	1 (20)	6 (55)	3 (27)
AST increased	2 (67)	2 (67)	1 (20)	1 (20)	6 (55)	2 (18)
ALP increased	2 (67)	0	0	0	3 (27)	2 (18)
Diarrhea	1 (33)	0	1 (20)	0	6 (55)	1 (9)
Arthralgia	1 (33)	0	0	0	2 (18)	0
Nausea	0	0	0	0	4 (36)	0
Fatigue	0	0	0	0	4 (36)	0
Hypokalemia	0	0	0	0	3 (27)	2 (18)
Decreased appetite	0	0	0	0	3 (27)	0
Headache	0	0	0	0	2 (18)	0
Hepatotoxicity	**2 (67)**	**2 (67)**	**2 (40)**	**1 (20)**	**6 (55)**	**5 (45)**

Overall safety data from lead-in and concurrent cohorts support lower dose sotorasib and lead-in administration for better tolerability

Li BT et al. IASLC 2022: Abstract OA03.06..

KRYSTAL-1 and KRYSTAL-7 Cohorts in NSCLC: Study Design

Key Eligibility Criteria

- Advanced, unresectable or metastatic NSCLC with $KRAS^{G12C}$ mutation[a]
- No prior systemic therapy for locally advanced/ metastatic disease
- Stable brain metastases allowed

KRYSTAL-1 Phase 1b

Adagrasib 400 mg[b] BID + Pembrolizumab
N=7

Key Study Objectives

- Primary endpoint: safety
- Secondary endpoints: ORR (RECIST v1.1), DOR, PFS, OS

KRYSTAL-7 Phase 2

Cohort 1a, PD-L1 TPS <1%[c,d]
Adagrasib 400 mg BID + Pembrolizumab
N=11

Cohort 2, PD-L1 TPS ≥1%[c]
Adagrasib 400 mg BID + Pembrolizumab
N=64

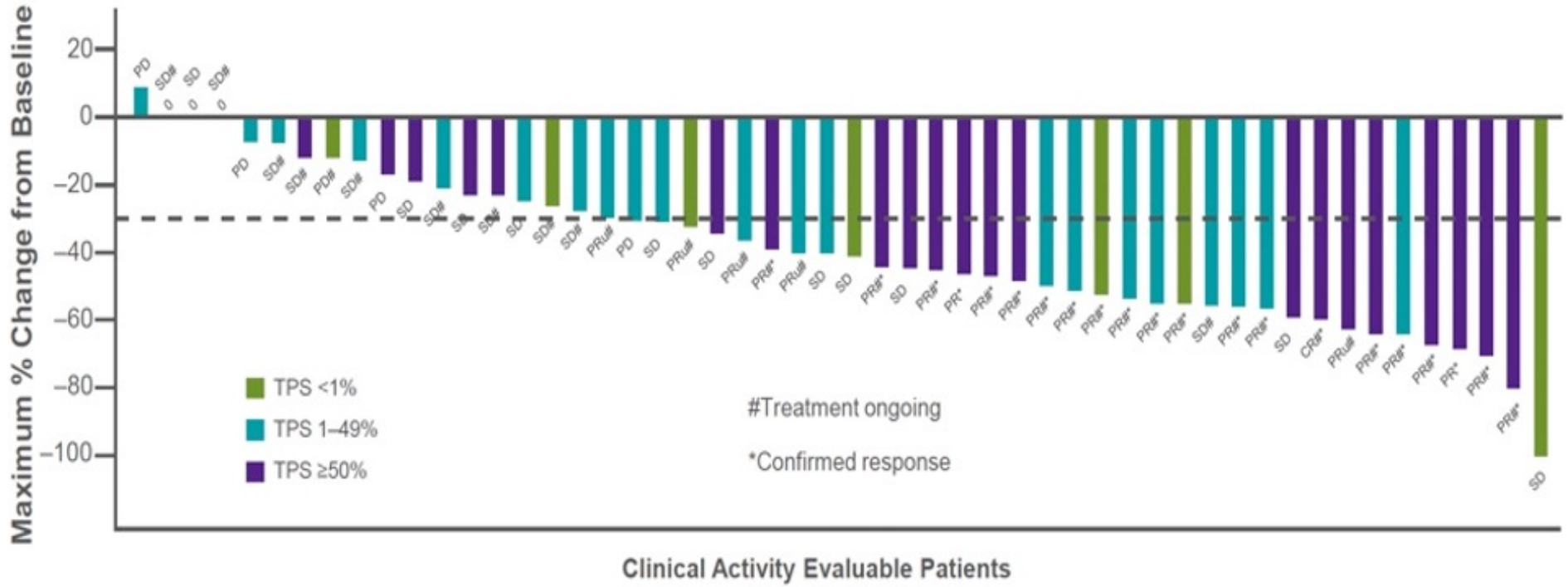
Key Study Objectives

- Primary endpoint: ORR (RECIST v1.1)
- Secondary endpoints: DOR, PFS, OS, safety, PK

- We report preliminary safety and efficacy data from a phase 1b cohort of KRYSTAL-1 and the phase 2 KRYSTAL-7 studies, evaluating adagrasib[e] 400 mg BID + pembrolizumab 200 mg IV Q3W in treatment-naïve patients with NSCLC harboring a $KRAS^{G12C}$ mutation
- KRYSTAL-1 median follow-up, 19.3 months; KRYSTAL-7 median follow-up 3.5 months

Janne PA et al. ESMO IO 2022: Abstract LBA4.

KRYSTAL-7 Cohort in NSCLC: Efficacy



- Objective responses were observed in 49% (26/53)[a] of patients across all PD-L1 levels, with a disease control rate of 89% (47/53)
- Responses were observed in 59% (13/22)[a] of patients with PD-L1 TPS ≥50%, 48% (10/21)[a] with PD-L1 TPS 1–49%, and 30% (3/10)[a] with PD-L1 TPS <1%

Janne PA et al. ESMO IO 2022: Abstract LBA4..

KRYSTAL-7 Cohort in NSCLC: Safety

Most Frequent TRAEs	Concurrent 400 mg BID Adagrasib + Pembrolizumab (n=75)				
TRAEs, %	**Any grade**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Any TRAEs	83%	15%	24%	40%	4%[a]
Most frequent TRAEs[b], %					
Nausea	48%	24%	19%	5%	0%
Diarrhea	43%	33%	5%	4%	0%
Vomiting	24%	13%	9%	1%	0%
ALT increased	21%	7%	7%	8%	0%
AST increased	21%	7%	5%	9%	0%
Fatigue	21%	9%	8%	4%	0%
Decreased appetite	20%	11%	9%	0%	0%
Amylase increased	16%	5%	11%	0%	0%

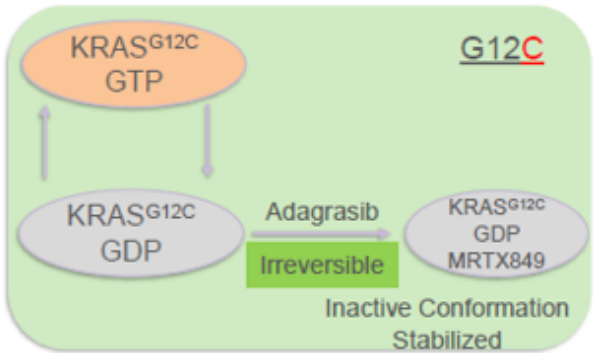
- There were no Grade 5 TRAEs
- Median time to onset for ALT increase and AST increase was 26 and 37 days, respectively; only 1 patient experienced new onset treatment-related ALT/AST increase after 3 months
- TRAEs led to adagrasib dose reduction in 23/75 (31%) patients and to dose interruption in 31/75 (41%) patients
- TRAEs led to discontinuation of both drugs in 2/75 (3%) patients and only pembrolizumab in 2/75 (3%)[c] patients

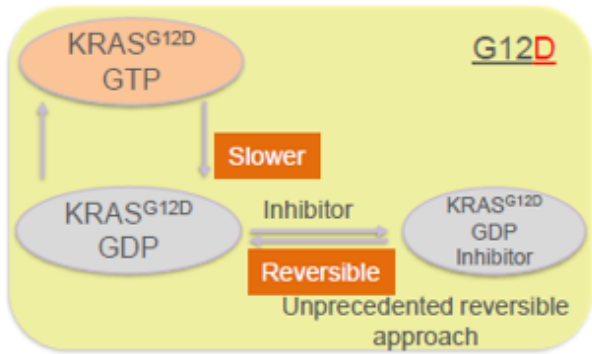
Janne PA et al. ESMO IO 2022: Abstract LBA4.

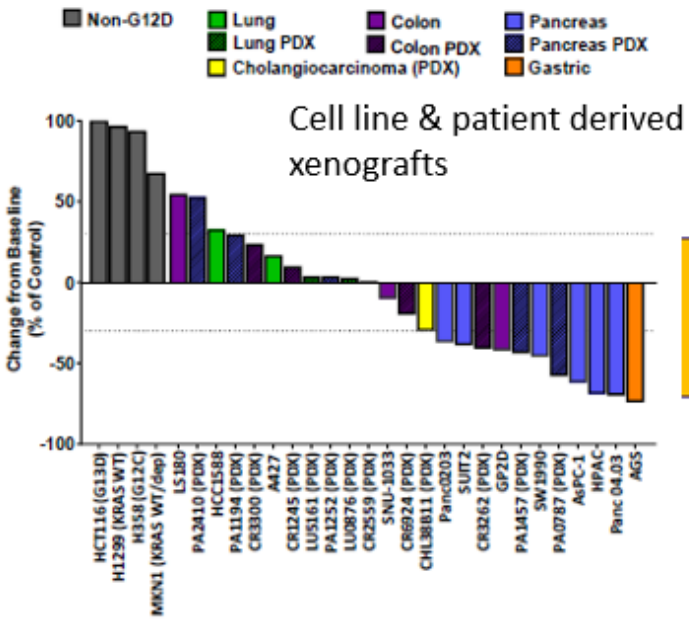
KRAS G12D Inhibitors

MRTX1133

- KRAS G12D 4% lung; 12% CRC,36% pancreatic
- Binds reversibly to KRAS G12D in both inactive (GDP bound; IC50 < 2 nM) & active (GTP bound state; IC50 9 nM) states
- > 100-fold selectivity over KRAS WT
- Pursuing formulations for IV delivery
- Other KRAS G12D inhibitor- RMC-9805 (Rev Med –RAS-ON), KRASG12D1-3 (BI)







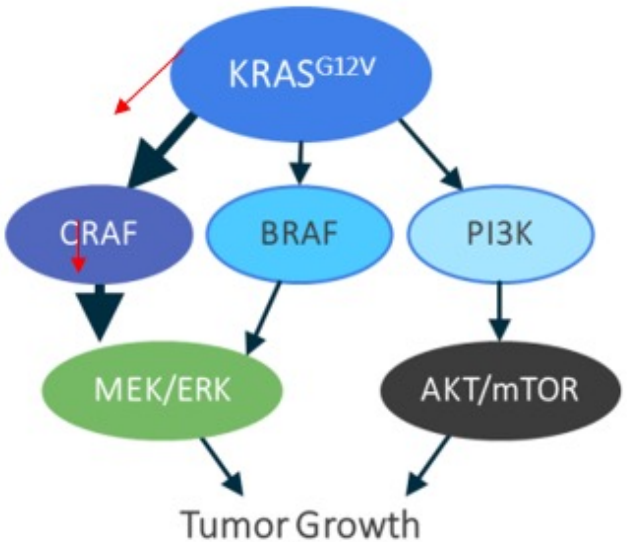
Cell line & patient derived xenografts

Regression in 15/25 (60%) models & response in 8/11 (73%) PDAC models and in 2/8 (25%) CRC models

Christensen J. AACR NCI-EORTC 2021. Hofmann MH et al. Cancer Discov. 2022 Apr 1;12(4):924-937.

Targeted Approach for KRAS G12V Lung Cancer – VS-6766 (RAF/MEK inhibitor) + Defactinib (FAK inhibitor)

VS-6766 inhibits CRAF- key driver of KRAS G12V

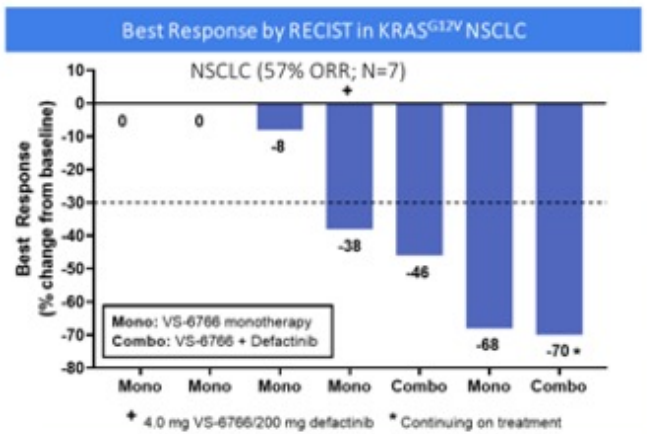


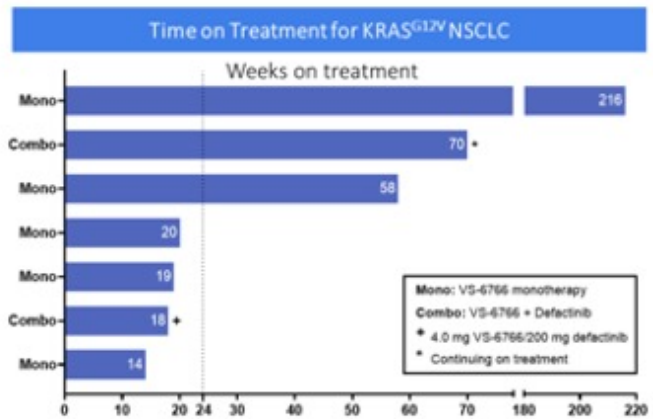
KRAS^{G12V} signals mainly through RAF/MEK in contrast to other variants, such as KRAS-G12D, which signal more through PI3K/AKT

KRAS^{G12V} models are especially dependent on CRAF

Pachter et al. WCLC 2021

Integrated Analysis –
7 pts, 4 response (**ORR 57% in KRAS G12V)**



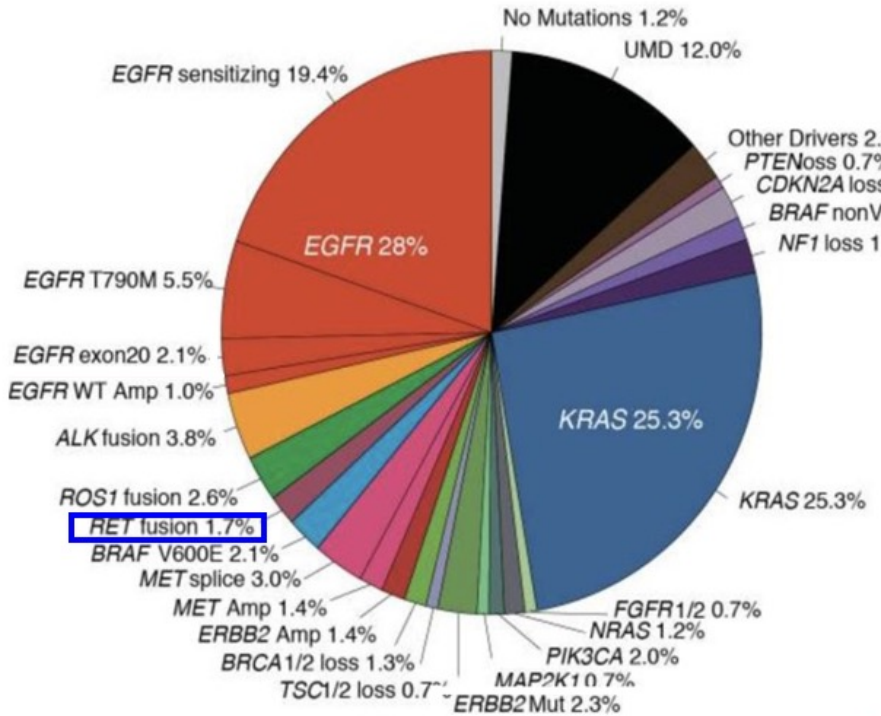


- Activity of VS-6766 as a single agent and in combo with defactinib in KRAS G12V mt NSCLC

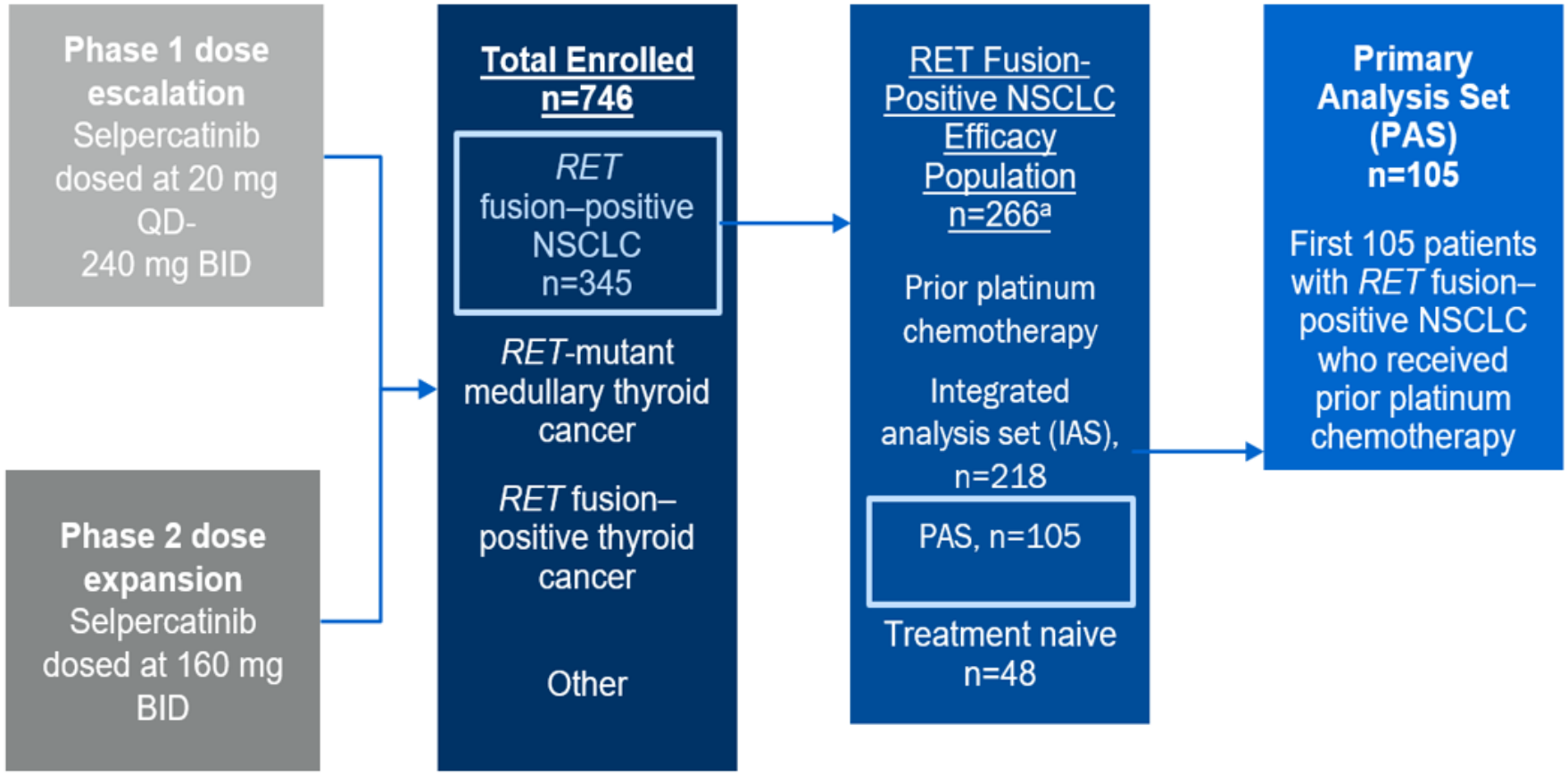
Source: [1] Guo, et al Lancet Oncology 2020 [2] Krebs, AACR April 2021(March 18, 2021 cutoff)

Registration-directed Phase 2 Study commenced December 2020 with an estimated Primary Completion Date for the Expansion Phase of March 2023 (clinicaltrials.gov)

RET Pathway


No Mutations 1.2%
UMD 12.0%
Other Drivers 2.9%
PTENoss 0.7%
CDKN2A loss 1.9%
BRAF nonV600E 1.3%
NF1 loss 1.9%
KRAS 25.3%
KRAS 25.3%
FGFR1/2 0.7%
NRAS 1.2%
PIK3CA 2.0%
MAP2K1 0.7%
ERBB2 Mut 2.3%
TSC1/2 loss 0.7%
BRCA1/2 loss 1.3%
ERBB2 Amp 1.4%
MET Amp 1.4%
METsplice 3.0%
BRAF V600E 2.1%
RET fusion 1.7%
ROS1 fusion 2.6%
ALK fusion 3.8%
EGFR WT Amp 1.0%
EGFR exon20 2.1%
EGFR T790M 5.5%
EGFR 28%
EGFR sensitizing 19.4%

LIBRETTO-001 Trial



- ***RET* alteration**
  - Determined by local CLIA (or similarly accredited) laboratories
- **Primary endpoint**
  - ORR (RECIST 1.1)
- **Secondary endpoints**
  - DOR
  - PFS
  - Safety
- **Treatment beyond progression permitted with continued benefit**

[a]Efficacy population includes all patients enrolled 6 months prior to data cutoff of March 2020, to allow adequate follow up.

Besse B, et al. Presented at ASCO 2021, June 4 – June 8, 2021, Virtual Format. Abstract 9065.

ARROW Trial

Eligibility criteria

- Age ≥18 years
- Unresectable locally advanced or metastatic solid tumor
- Documented *RET* fusion or mutation (local testing)
- Measurable disease per RECIST v1.1
- ECOG PS 0-1

Phase 1 dose escalation (completed)
Phase 2 dose determined
400 mg once daily

Phase 2 dose expansion (ongoing)
Groups defined by disease type and prior therapy, treated at phase 2 dose

1º endpoints

- ORR (BICR per RECIST v1.1)
- Safety

Key 2º endpoints

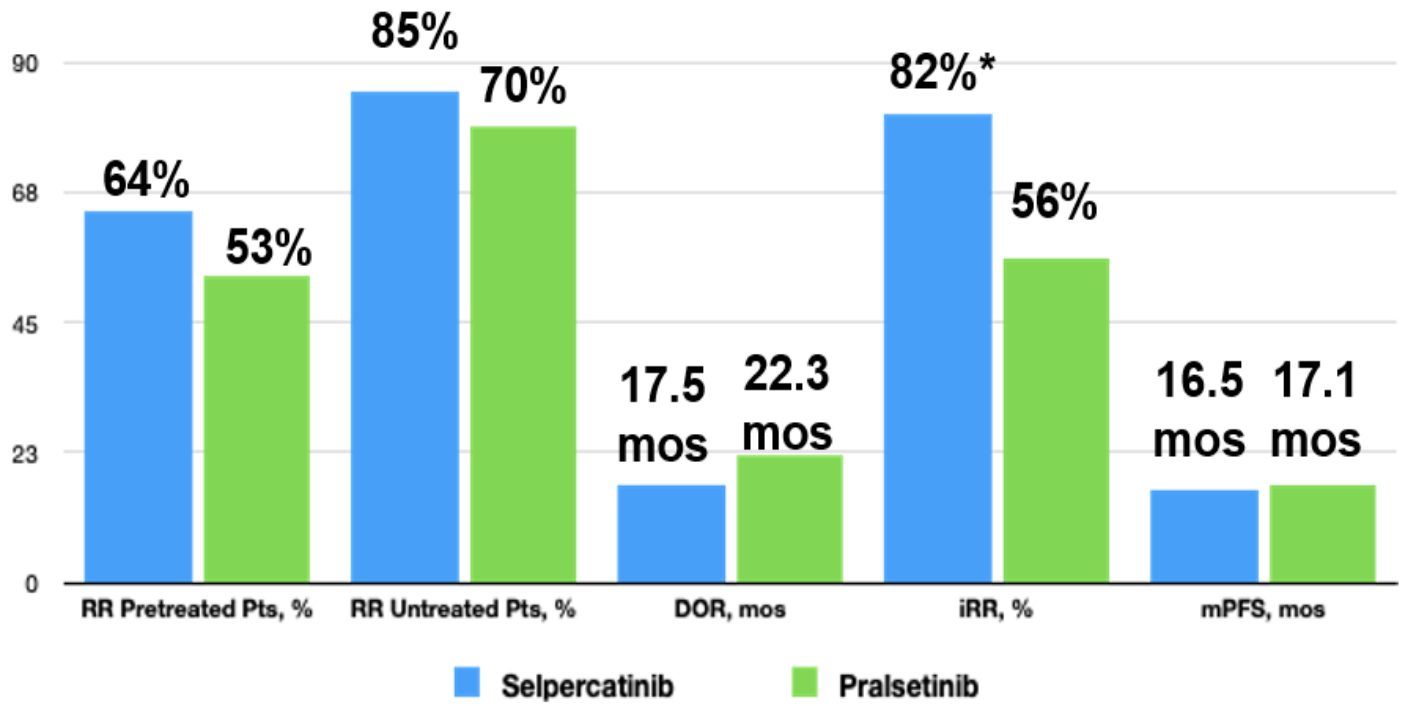
- DOR
- CBR[a]
- DCR
- Intracranial response rate
- PFS
- OS

	Baseline Characteristics (Efficacy Population)	
	Prior Platinum (n=92)	Treatment Naive (n=29)
Med age (range), y	60 (53-68)	65 (54-69)
Female	50%	52%
Median lines of prior therapy (range)	2 (1-3)	0
Brain metastases	41%	41%
RET Fusion Partner		
KIF5B	75%	69%
CCDC6	17%	10%
Other	2%	0%
Unknown	5%	21%

[a] Complete or partial response or stable disease of ≥16 weeks.
Gainor JF, et al. *Lancet Oncol*. 2021 Jul;22(7):959-969.

RET Inhibition in Practice

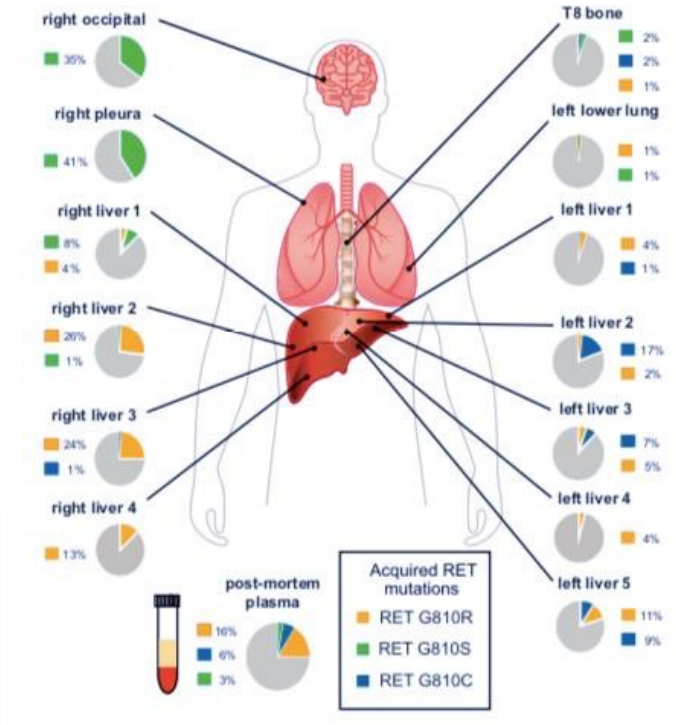
Efficacy of Selpercatinib and Pralsetinib in in *RET*+ NSCLC



Drilon A, et al. NEJM 2020; Gainor J, et al. Lancet Oncol 2021

*measurable disease

Acquired resistance to RET inhibitors



Solomon B, et al. JTO 2020

LIBRETTO-001: Adverse Events in 746 Patients With *RET*-Altered Cancers (≥15% Occurrence)

	AEs, Regardless of Attribution		Treatment-Related AEs	
	Any grade (%)	Grades 3-4 (%)	Any grade (%)	Grades 3-4 (%)
Dry mouth	40	0	36	0
Diarrhea	39	3[a]	22	2[a]
Hypertension	37	19	25	12
ALT increased	33	10	26	8 ★
AST increased	33	9	26	7 ★
Fatigue	31	1[a]	19	1[a]
Constipation	27	<1[a]	13	<1[a]
Peripheral edema	26	<1[a]	14	0
Headache	24	1[a]	9	<1[a]
Nausea	23	<1[a]	10	<1[a]
Blood creatinine increased	21	<1[a]	12	0
Abdominal pain	20	2[a]	6	<1[a]
Rash	19	<1[a]	12	<1[a]
Prolonged QT	18	4[a]	14	3[a]
Cough	16	0	1	0
Vomiting	16	<1[a]	4	<1[a]
Dyspnea	15	3	2	0

- 2% of patients discontinued due to treatment-related adverse events

ARROW: Treatment-Related Adverse Events in ≥10% of Patients (N=471, All Tumor Types)

AE Preferred Term	All Patients (n=354)	
	Any grade	Grade ≥3
Neutropenia	40%	19%
AST increased	39%	3%
Anemia	35%	13%
White blood cell count decreased	32%	★ 8%
ALT increased	28%	2%
Hypertension	26%	12%
Constipation	26%	1%
Asthenia	25%	3%
Lymphopenia	18%	11%
Hyperphosphatemia	17%	0%
Diarrhea	16%	1%
Thrombocytopenia	15%	4%
Blood creatinine increased	15%	0%
Dysgeusia	14%	0%
Blood creatine phosphokinase increased	14%	6%
Edema	14%	0%
Dry mouth	13%	0%
Pneumonitis	11%	3%

- 6% of patients discontinued due to treatment-related adverse events

Safety population included all patients with RET-altered cancers (includes RET-mutant MTC and RET-fusion positive NSCLC). In total, 25 of 746 patients had grade 5 TEAEs. No grade 5 TRAEs were observed. Safety among the 345 patients with NSCLC was consistent with the safety of the overall population. Data cutoff March 2020. [a]Only grade 3 AEs occurred, no grade 4 AEs.
Besse B, et al. Presented at ASCO 2021, June 4 – June 8, 2021, Virtual Format. Abstract 9065.

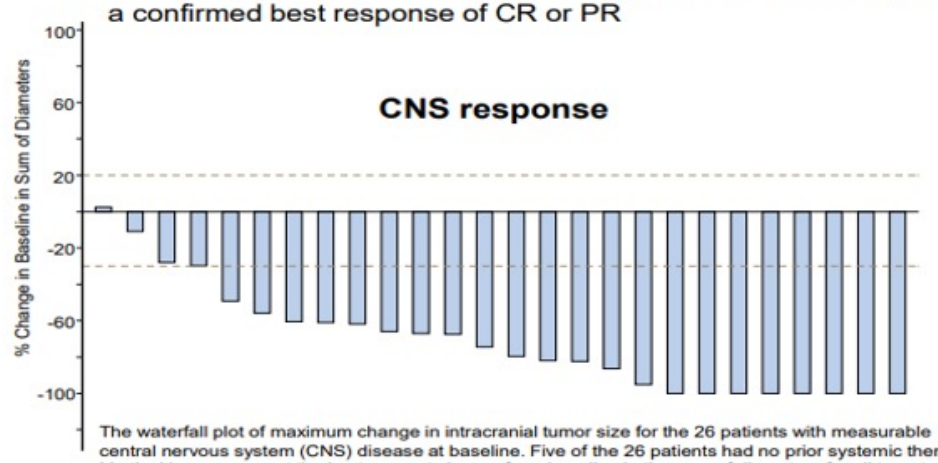
Curigliano G, et al. Presented at ASCO 2021, June 4 – June 8, 2021, Virtual Format.

GenesisCare OLA FLASCO FAU MEDICINE FLORIDA ATLANTIC UNIVERSITY

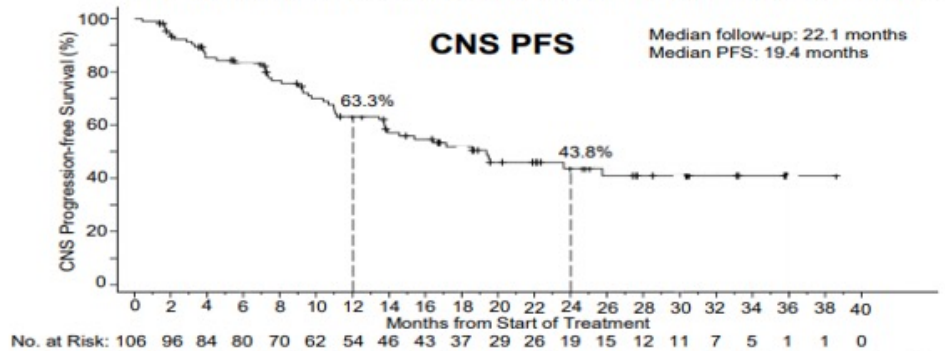
Durability of Efficacy and Safety with Selpercatinib in Patients with RET Fusion+ Non-Small-Cell Lung Cancer: LIBRETTO-001

CNS Response

- Of the 26 patients with measurable CNS disease at baseline, 22 had a confirmed best response of CR or PR



The waterfall plot of maximum change in intracranial tumor size for the 26 patients with measurable central nervous system (CNS) disease at baseline. Five of the 26 patients had no prior systemic therapy. Vertical bars represent the best percent change from baseline in the sum of diameters for all target lesions. Progressive disease (+20%) and partial response (-30%) are indicated with the dashed lines.



Intracranial PFS is shown for the 106 patients with measurable or non-measurable CNS disease at baseline among the 355 NSCLC patients of the efficacy population.

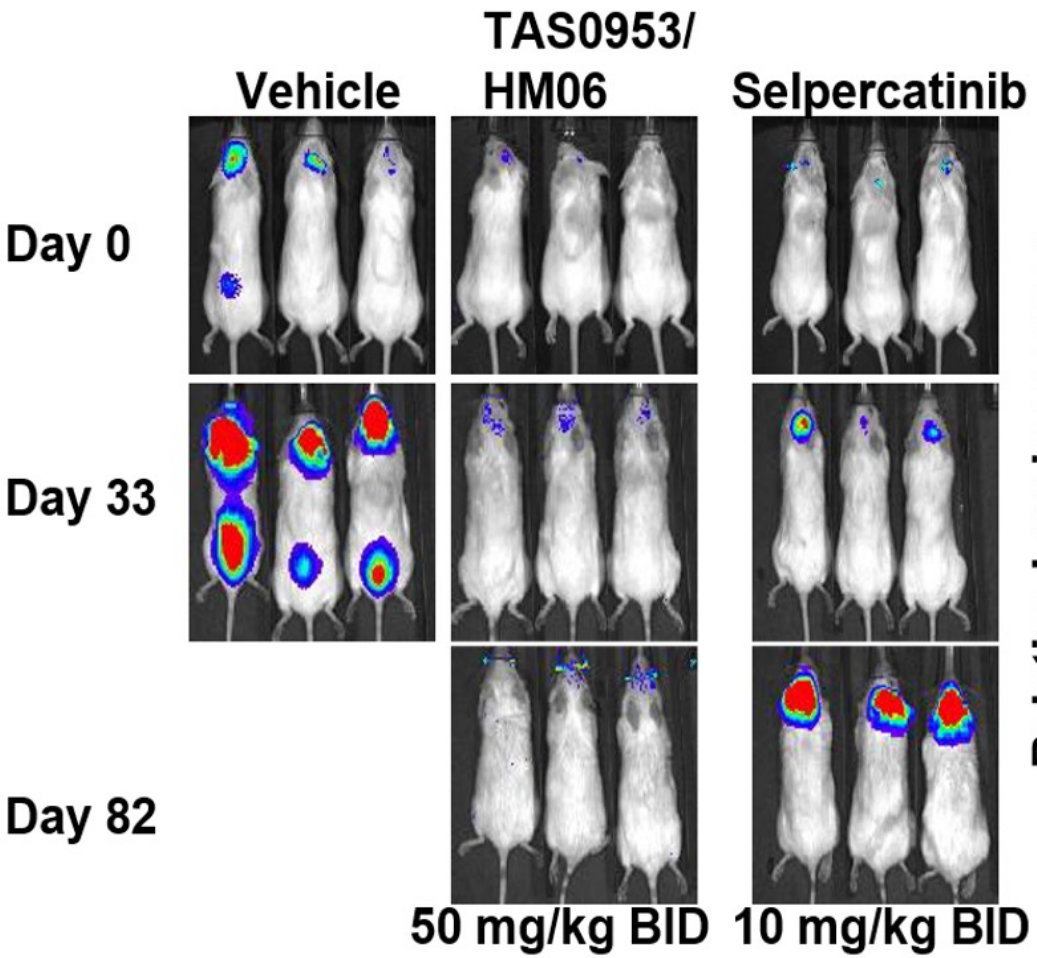
CNS ORR: 85%

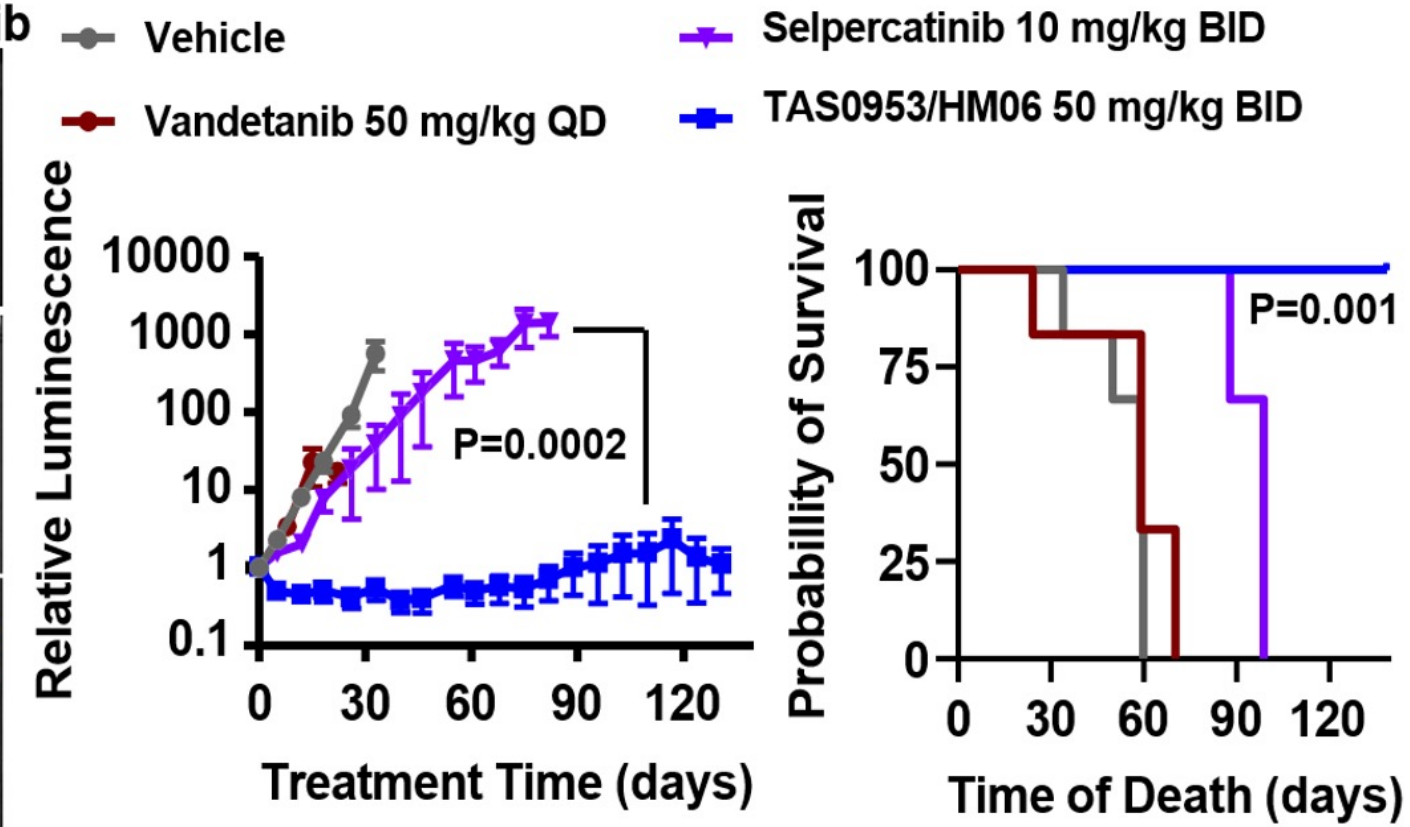
Drillon A et al. P27. 12th European Lung Cancer Conference (ELCC); Prague, Czech Republic; 30 March – 2 April, 2022.

Let's discover novel RET inhibitors

Drug	CNS Penetration	Activity against V804 mutations	Activity against G810 mutations	Phase of development
BOS172738/DS-5010 Zeteletinib	✓	+	-	Ph. I – NCT03780517 Treatment naïve Dose escalation data reported
TPX-0046 Enbenzotinib	✓	+	+	Preclinical data available Ph. I/II ongoing NCT04161391 TKI-naïve and pretreated
LOXO- 260	✓	+	+	Preclinical data available Ph. I/II ongoing NCT05241834 TKI-pretreated
TAS0953/HM06 Vepafestinib	See next slides			

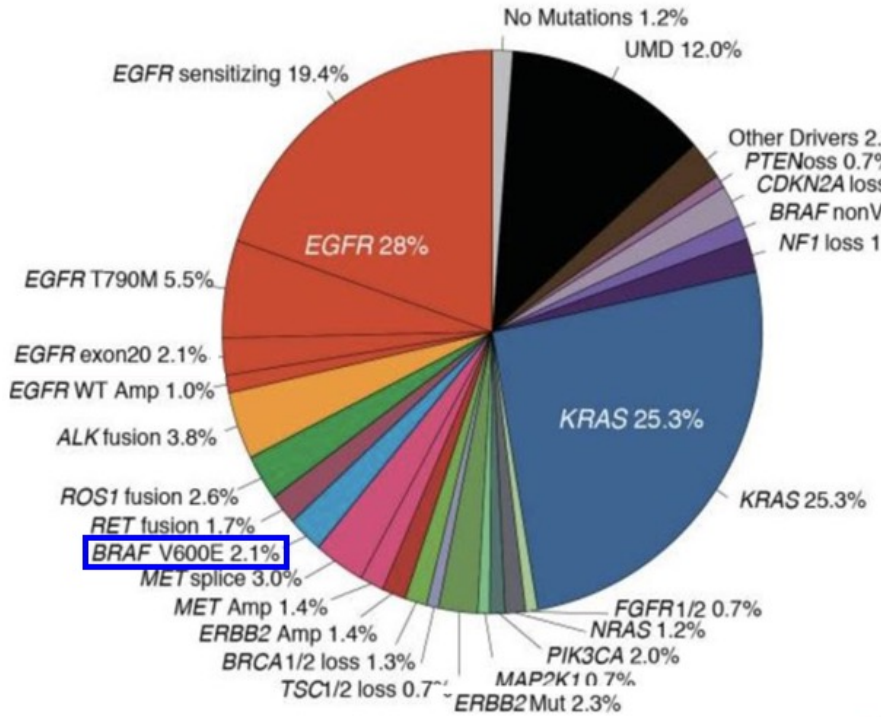
TAS0953/HM06 is more Effective than Selpercatinib in the CNS





Somewar R, WCLC 2022

B-RAF Pathway



Study Design: Dabrafenib plus Trametinib in Patients with B-RAF V600E Metastatic Non-Small Cell Lung Cancer

Key Eligibility Criteria[1-3]

- *BRAF* V600E metastatic NSCLC
- No prior exposure to BRAF or MEK inhibitor
- Absence of *EGFR* mutation or *ALK* rearrangement[a]
- Adult patients (≥18 years of age)

N=171

Cohort A
Previously treated patients
Dabrafenib 150 mg po twice daily
(n=78)

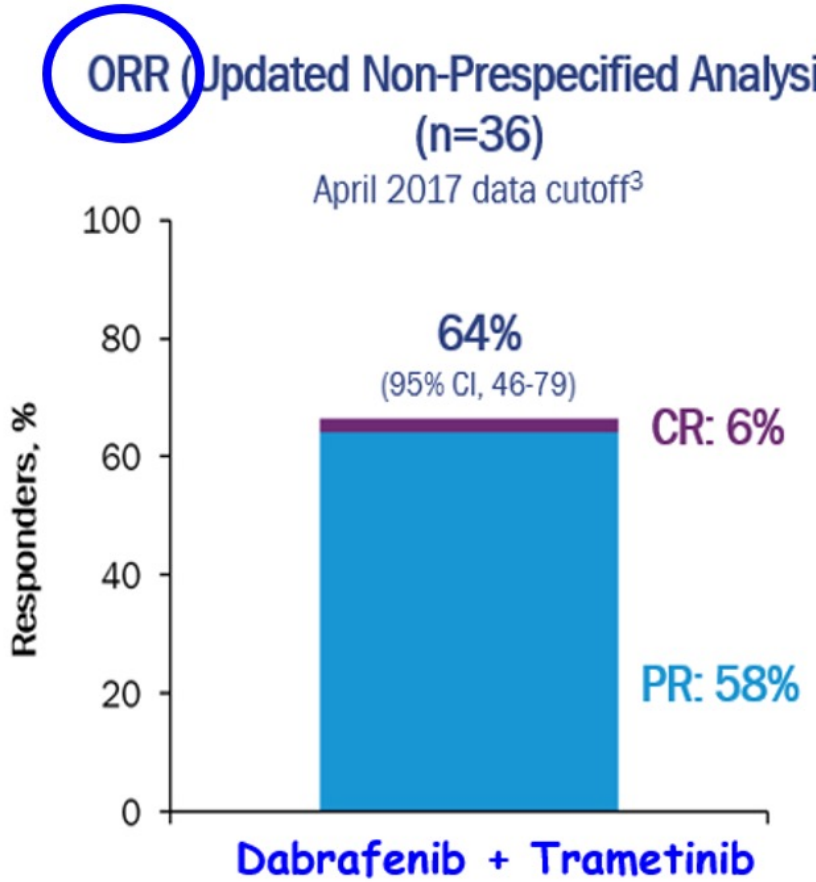
Cohort B
Previously treated patients
Dabrafenib 150 mg po twice daily
Trametinib 2 mg po daily
(n=57)

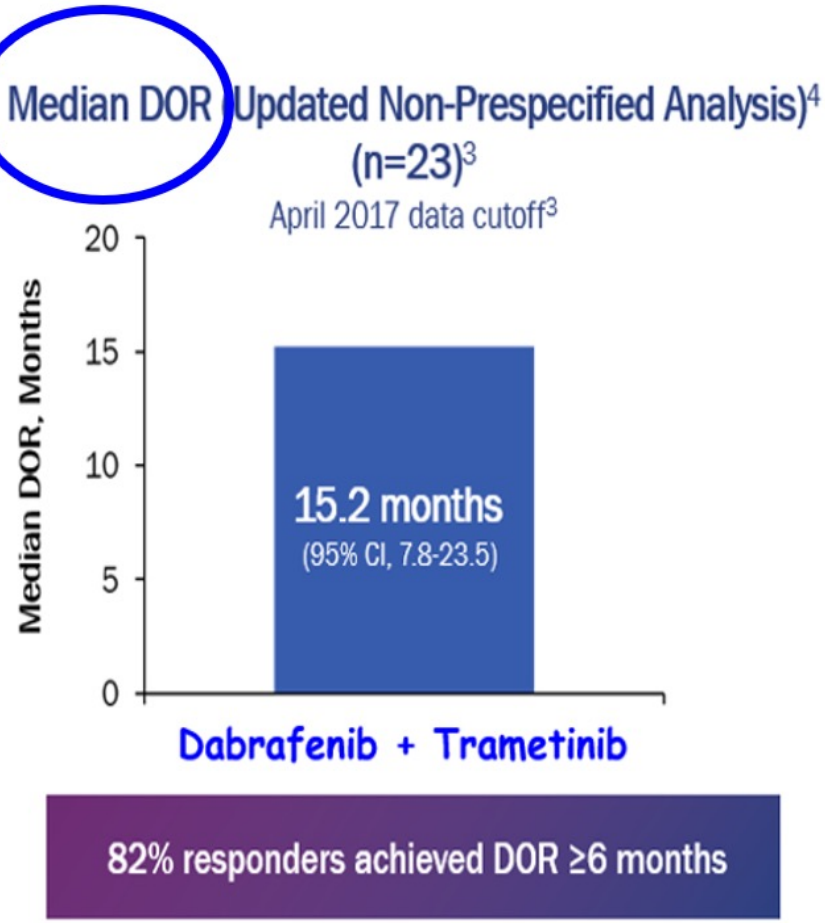
Cohort C
First line patients
Dabrafenib 150 mg po twice daily
Trametinib 2 mg po daily
(n=36)

- Major efficacy outcomes: ORR, DOR[1,2,a,b]
- Additional outcomes[3-5,a,b]
  - OS, PFS, safety

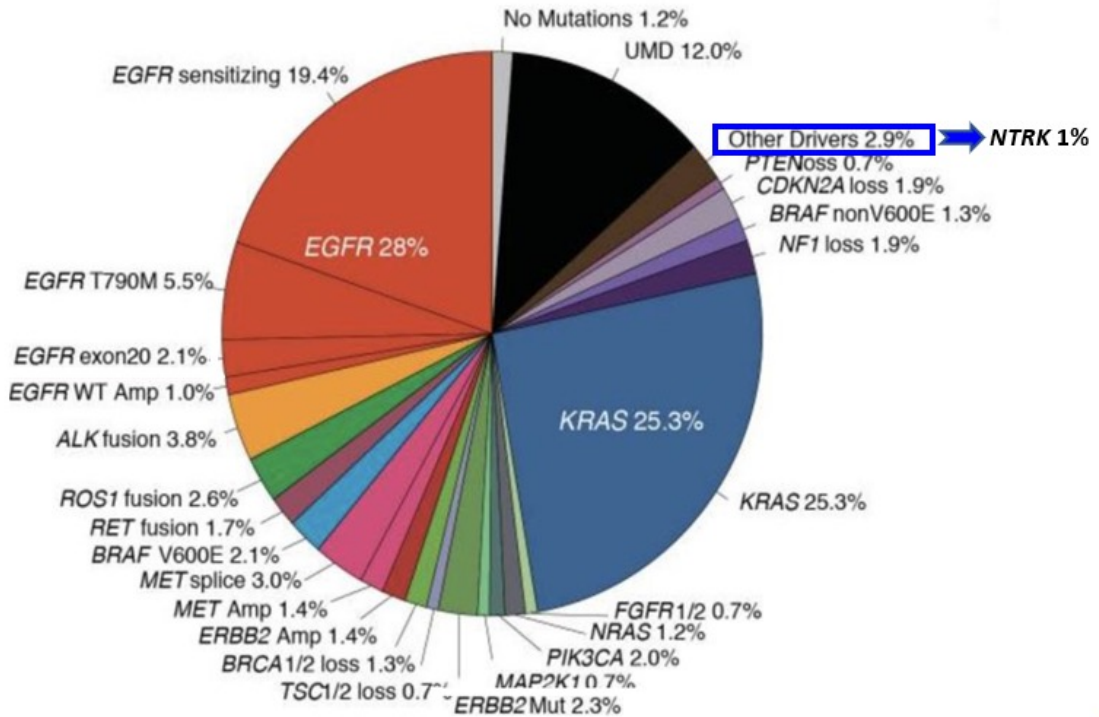
A phase 2, multicenter, non-randomized, non-comparative, open-label trial

First-Line: Dabrafenib + Trametinib in Patients with B-Raf V600E Metastatic NSCLC: ORR & DOR





NTRK Pathway

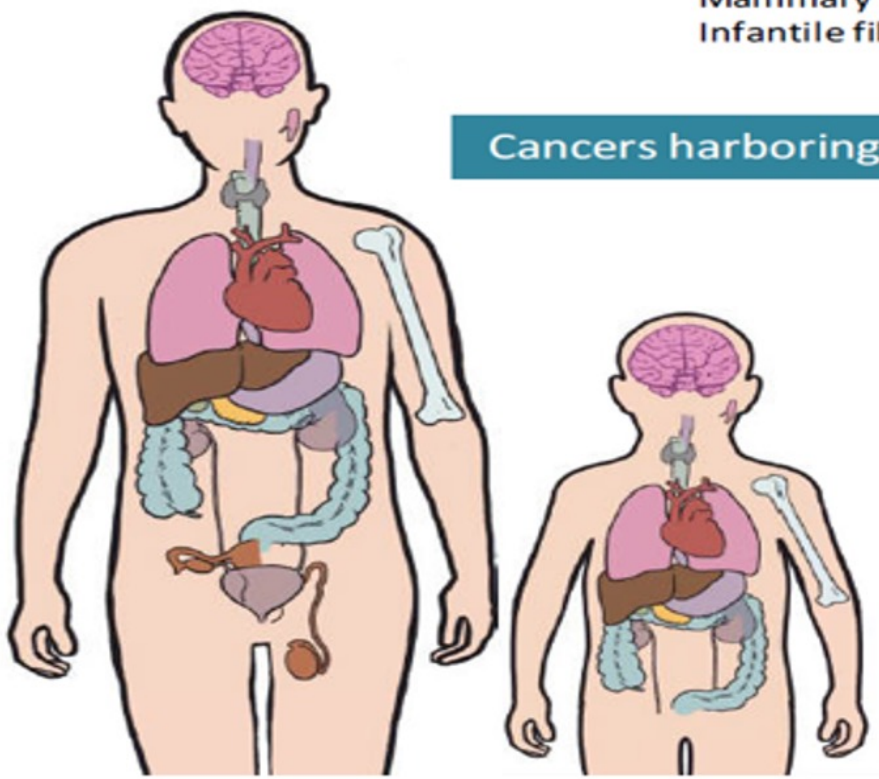


NTRK fusions are found in diverse cancers including lung cancers

Cancers enriched for TRK fusions

Secretory breast carcinoma
Mammary analogue secretory carcinoma
Infantile fibrosarcoma

Frequency
75% to >90%



Cancers harboring TRK fusions at lower frequencies

Congenital mesoblastic nephroma
Pontine glioma
Spitzoid melanoma
Thyroid Cancer
GIST ("pan-negative")

Frequency
5% to 25%

Lung cancer
Other sarcomas
Astrocytoma/Glioblastoma
Colorectal cancer
Cholangiocarcinoma
Pancreatic cancer
Head and neck squamous cancer
Breast cancer
Melanoma

Frequency
<1% to <5%

Estimated 1,500–5,000 patients harbor TRK fusion-positive cancers in the United States annually

GenesisCare

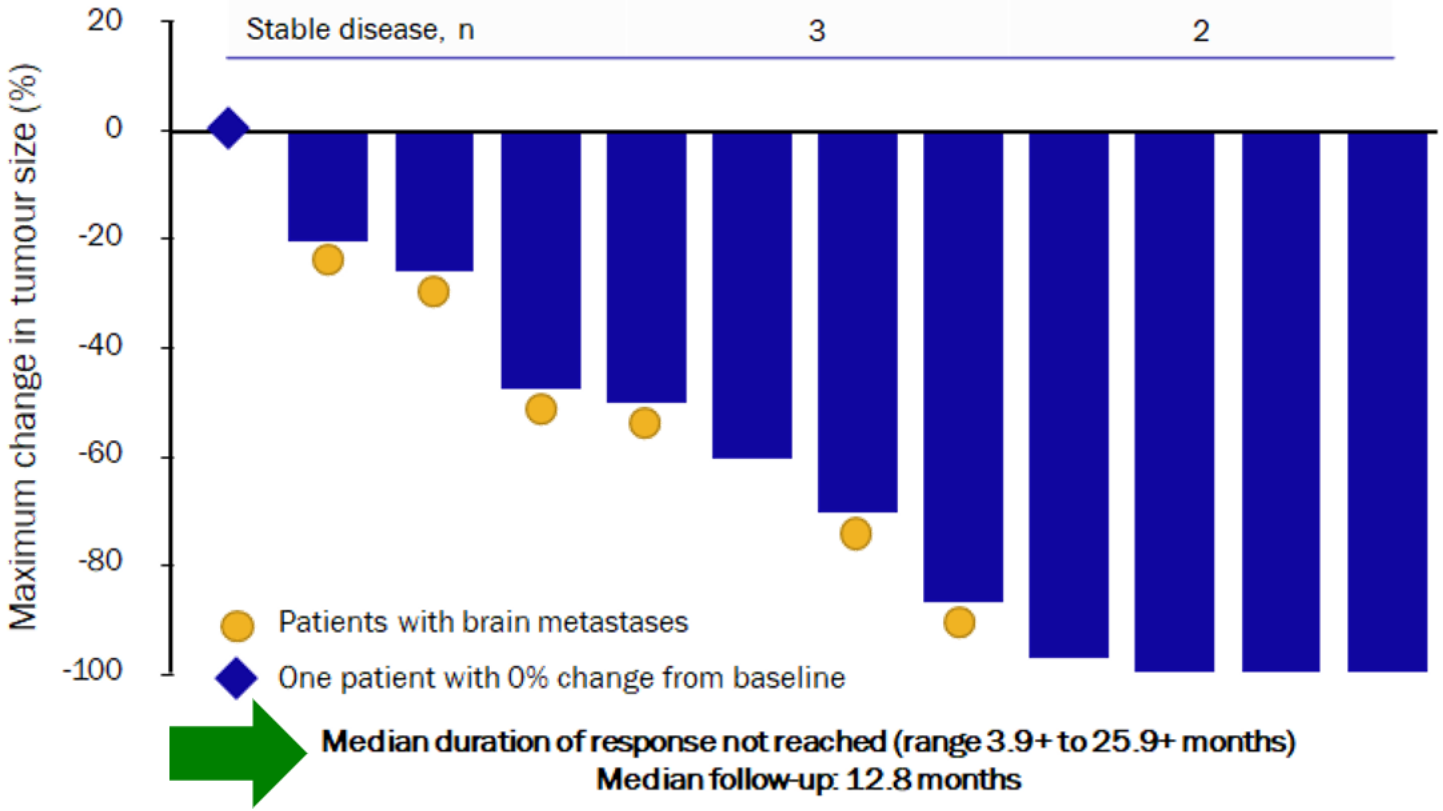
OLA
Oncology Latin American Association

FLASCO

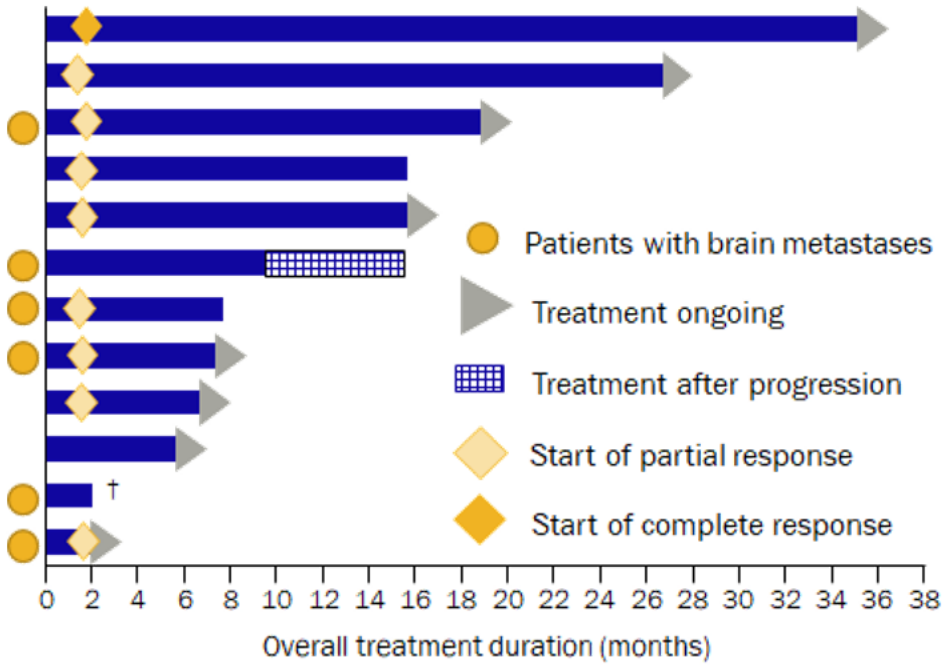
FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

Larotrectinib is active in TRK fusion lung cancer

	All lung cancer patients (n=12)	Patients with brain metastases (n=6)
Objective response rate (%)	**75%**	**67%**
Complete response, n	1	0
Partial response, n	8*	4*
Stable disease, n	3	2



Median duration of response not reached (range 3.9+ to 25.9+ months)
Median follow-up: 12.8 months

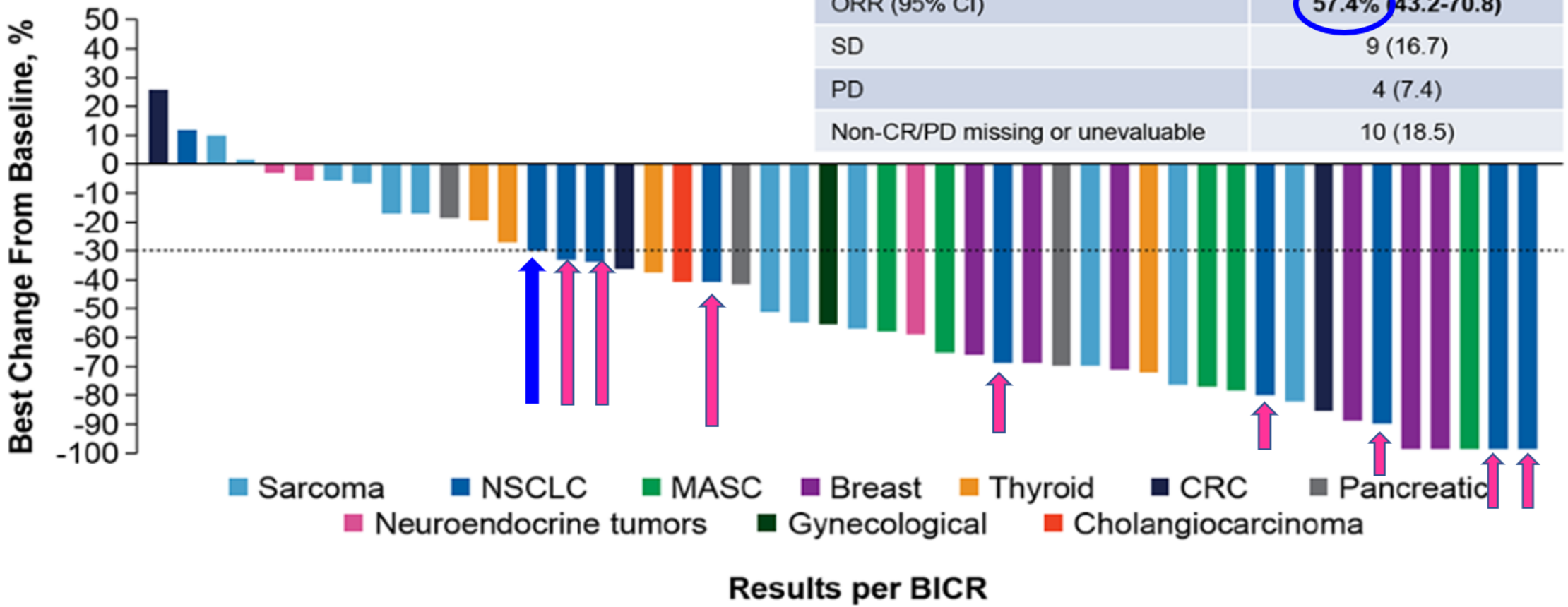


Duration of response: 1.8+ to 35.2+ months

Data cut-off: 19 February 2019. *Partial response pending confirmation in one patient. †Nontarget progressive disease in asymptomatic leptomeningeal focus. Investigator assessments as of data cut-off date. TRK, tropomyosin receptor kinase. Farago AF, et al. Presented at the World Conference on Lung Cancer. September 2019. Barcelona, Spain. Abstract MA09.07.2.

Entrectinib Activity in *NTRK* Fusion-Positive Solid Tumors: Individual Patient Responses by Tumor Type[1]

	NTRK+ Patients (n = 54)
ORR (95% CI)	**57.4% (43.2-70.8)**
SD	9 (16.7)
PD	4 (7.4)
Non-CR/PD missing or unevaluable	10 (18.5)



1. Demetri GD et al. ESMO 2018. Abstract LBA17.

Conclusions

- Sotorasib met its primary endpoint in CodeBreak 200 study by improving PFS over docetaxel in second line for KRAS G12C mutant tumors.
- Combination of KRAS G12C inhibitors with CPI looks promising.
- Novel KRAS inhibitors against G12D and G12V are in development.
- Dabrafenib/trametinib and selpercatinib got approval by US FDA for solid tumors which harbor BRAF V600E and RET genomic alterations, respectively.
- RET, MET and NTRK are agnostic biomarkers.
- **Testing ALL non-Squamous NSCLC with NGS DNA and RNA platforms is the key to deliver not only personalized medicine, but the best therapy upfront.**

Thank You !

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